題名:Anti-angiogenic action of 5; 5-diphenyl-2-thiohydantoin-N10 (DPTH-N10).

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摘要:Previously, we demonstrated that 5,5-diphenyl-2-thiohydantoin (DPTH) exerts an anti-proliferation effect on subcultured human umbilical vein endothelial cells (HUVEC). In the present study, we show that 2(naphthalen-2-ylmethylsulfanyl)-5,5-diphenyl-1,5-dihydro-imidazol-4-one (DPTH-N10), a derivative compound of DPTH, exerts a 5 times stronger inhibition of [3H]thymidine incorporation into HUVEC as compared with DPTH and at very low concentrations (0-20 microM) inhibited DNA synthesis and decreased cell number in cultured HUVEC in a concentration- and time-dependent manner, but not in human fibroblasts. [3H]thymidine incorporation analysis demonstrated that treatment of HUVEC with DPTH-N10 arrested the cell at the G0/G1 phase of the cell cycle. Western blot analysis revealed that the protein level of p21 in HUVEC increased after DPTH-N10 treatment. In contrast, the protein levels of p27, p53, cyclins A, D1, D3 and E, cyclin-dependent kinase (CDK)2, and CDK4 in HUVEC were not changed significantly after DPTH-N10 treatment. Immunoprecipitation showed that the formation of the CDK2-p21 complex, but not the CDK2-p27, CDK4-p21, and CDK4-p27 complex, was increased in the DPTH-N10-treated HUVEC. Kinase assay further demonstrated that CDK2, but not CDK4, kinase activity was decreased in the DPTH-N10-treated HUVEC. Pretreatment of HUVEC with a p21, but not p27, antisense oligonucleotide reversed the DPTH-N10-induced inhibition of [3H]thymidine incorporation into HUVEC. Taken together, these data suggest that DPTH-N10 inhibits

HUVEC proliferation by increasing the level of p21 protein, which in turn inhibits CDK2 kinase activity, and finally interrupts the cell cycle. Capillary-like tube formation, aortic ring culture, and chick embryo chorioallantoic membrane (CAM) assays further demonstrated the anti-angiogenic effect of DPTH-N10.